Medical & heathcare, Drug discovery

Monolayer platform using human biopsy-derived small intestinal organoids for pharmaceutical research

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Abstract

The human small intestine is the key organ for absorption, metabolism, and excretion of orally administered drugs. To preclinically predict these reactions in drug discovery research, a cell model that can precisely recapitulate the *in vivo* human intestinal monolayer is desired. Here, we developed a monolayer platform using human biopsy-derived small intestinal organoids for application to pharmacokinetic studies. The human small intestinal organoid-derived monolayer was prepared by a simple method in 3–8 days. It consisted of polarized absorptive cells and had tight junctions. It showed much higher drug-metabolizing enzyme activities than the existing models (Caco-2 cells). It also showed transporter activity. Based on these findings, this monolayer assay system using biopsy-derived human small intestinal organoids is likely to be widely adopted.

Background & Results

The human small intestine plays a central role in the pharmacokinetics of orally administrated drugs, which account for around 70% of FDA-approved drugs (U. S. Food and Drug Administration, 2019). The process of absorbing, metabolizing, and excreting of orally administered drugs begins in the small intestine. These series of reactions are called the first-pass effect and are an essential consideration in drug discovery research. An *in vitro* system to recapitulate the human *in vivo* drug absorption, metabolism, and excretion is crucially important for the structural design of compounds in the early stages of drug discovery research.

It has been difficult to culture primary human intestinal epithelial cells for a long period without diminishing their functions and viability. Therefore, small intestinal tissues obtained from rodents or a human colon cancer-derived cell line, *i.e.,* Caco-2 cells, have been broadly used and have made a major contribution to pharmacokinetic studies. Nonetheless, the former has the problem of species differences, and the latter has the problem that some of the drug-metabolizing enzymes and drug transporters are absent or poorly expressed in Caco-2 cells. To solve these problems, an alternative system is urgently needed.

We successfully produced a monolayer from biopsy-derived human small intestinal organoids by means of a very simple and straightforward method. Organoids are self-organized three-dimensional tissue cultures. They can proliferate, be passaged, and maintained for a long period in *in vitro* culture. The human small intestinal organoid-derived monolayer can be generated from the organoids in 3–8 days by using a single medium without complicated procedures (Fig.1). The monolayer showed higher expressions and functions of major pharmacokinetic-related enzymes and transporters than Caco-2 cells, and these profiles in the monolayer were close to those of the human intestine in general. In addition, the human small intestinal organoid-derived monolayer exhibited gene expression profiles similar to those of the adult small intestine (Fig.2).

Significance of the research and Future perspective

The human small intestinal organoid-derived monolayer can recapitulate the characteristics of the *in vivo* small intestine, and therefore this monolayer could be a powerful tool to predict the pharmacokinetics of orally administered drugs.

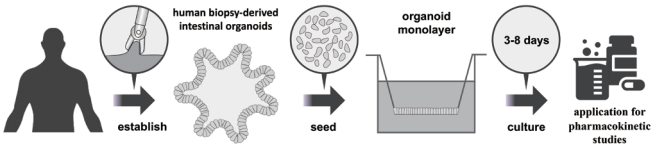

Fig 1. Graphical abstract of this study

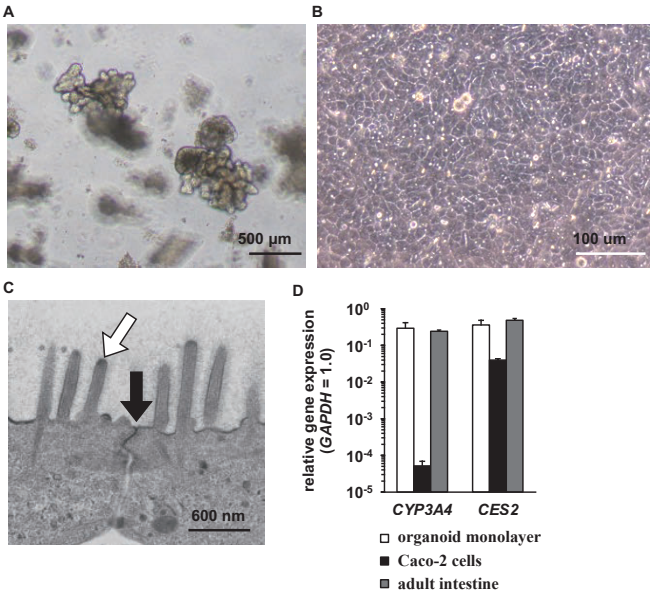

Fig 2. Characteristics of human small intestinal organoids
(A) Established human small intestinal organoids
(B) Human small intestinal organoids-derived monolayer
(C) Transmission electron micrographs of the monolayer. A brush border with microvilli (white arrow) and tight junctions (black arrow) were observed.
(D) The gene expression levels of the major drug-metabolizing enzymes (CYP3A4 and CES2) in the human small intestinal organoids-derived monolayer were compared with those in Caco-2 cells and human adult intestine.

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